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ORIGINAL ARTICLE

Synthesis of tetrahydrobenzo[b]pyran under catalysis of $NH_4Al(SO_4)_2{\cdot}12H_2O$ (Alum)

Ali A. Mohammadi [a,*], Mohammad R. Asghariganjeh [b], Armin Hadadzahmatkesh [a]

[a] *Department of Chemistry, Islamic Azad University, Sabzevar Branch, Sabzevar, Iran*
[b] *Department of Chemistry, Islamic Azad University, Omidieh Branch, Omidieh, Iran*

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KEYWORDS

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Dimedone;
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Multi component reaction;
$NH_4Al(SO_4)_2{\cdot}12H_2O$ (Alum)

Abstract A simple and efficient one-pot synthesis of tetrahydrobenzo[b]pyrans from the three-component reaction between dimedone, aldehydes, and active methylene compounds using $NH_4Al(SO_4)_2{\cdot}12H_2O$ (Alum) as a catalyst at 80 °C is described. The catalyst exhibits remarkable reactivity and is reusable.

1. Introduction

Multi-component reactions (MCRs) are emerging as important tools for efficient synthesis of a wide variety of organic molecules (Domling and Ugi, 2000). Such reactions offer a number of practical, environmental, and economical advantages for construction of complex molecular architectures over the more traditional approaches. While numerous MCRs have been devised, relatively few processes that result in the formation of two or more intermolecular carbon–carbon bonds are known.

4*H*-pyrans belong to an important class of heterocyclic compounds having important biological activities (Green et al., 1995). They are reported to have diverse pharmacological activities such as anti-coagulant, anti-cancer, spasmolytic, diuretic, anti-ancaphylactia (Weber et al., 1999), Alzheimer's disease, AIDs associated dementia and myoclonus (Konkoy et al., 2001). They are also reported to serve as an important regulator for potassium cation channel (Sun et al., 1997) and photochemical activities (Armetso et al., 1989).

Because of the intense interest in the biological activity of these compounds, several improved procedures for the synthesis of pyrans were reported. One of the most important methods for the synthesis of these compounds is one-pot condensation of an aldehyde, dimedone and malononitrile. Various catalysts such as acetic acid (Kamaljit et al., 1996), $CeMgxZr_1$-xO_2 (Rathod et al., 2010), HTMAB (Jin et al., 2004), TEBA (Shi et al., 2003), DBSA (Jin et al., 2004), basic quaternary ammonium salt (Zhao et al., 2010), $RE(PFO)_3$ Wang et al., 2006, and s-proline (Balalaie et al., 2006) have been used for this reaction. Some of them are very fascinating from a synthetic chemist's point of view. Despite their tremendous success, some drawbacks still remain for example, reacting at high temperature, expensive catalysts, etc. In order to circumvent these obstacles, we decided to reconsider developed new synthetic routes. The results are represented in the following section.

* Corresponding author. Tel.: +98 571 2646810.
E-mail address: Aliamohammadi@iaus.ac.ir (A.A. Mohammadi).
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2. Results and discussion

Very recently, we reported the preparation of quinazolinediones (Azizian et al., 2003a), γ-spiroiminolactiones (Azizian et al., 2003b), pyroles (Azizian et al., 2003c), and *cis*-isoquinolonic acid (Azizian et al., 2005) via the respective multi-component reactions. Along this line, we designed a new method for the three-component synthesis of tetrahydrobenzo[b]pyrans in one step. In this direction, the use of relatively heterogeneous, nontoxic and inexpensive $NH_4Al(SO_4)_2{\cdot}12H_2O$ (Alum) was taken as the center of our study (Azizian et al., 2005; Mohammadi et al., 2008). In the course of our research on the application of heterogeneous catalysts in organic reactions, we have found that alum is an effective promoter for the preparation of tetrahydrobenzo[b]pyrans.

In addition, we have found that the one-pot condensation of dimedone **1**, aldehydes **2a-t**, and active methylene compounds (meldrum's acid, malononitrile, ethyl and methyl cyanoacetate and indandione) in the presence of a catalytic amount of Alum results in a rapid formation of the corresponding tetrahydrobenzo[b]pyran **4a-t** when the reaction mixtures were heated with stirring at 80 °C (Schemes 1 and 2) (Table 1).

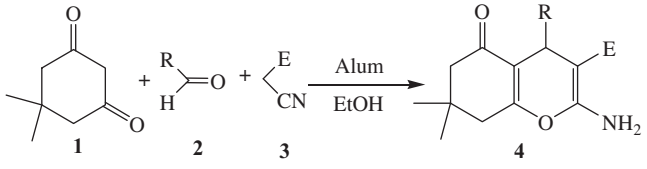
Furthermore, it is remarkable to note that the condensation proceeds with a slight amount of catalyst concentration (20 mol%, Alum) at ambient conditions and gives tetrahydrobenzo[b]pyrans in good yields. Interestingly, the heterogeneous catalyst was not deactivated and could be reused several times. Five consecutive runs of the reaction of dimedone, benzaldehyde and malononitrile with Alum were carried out (Fig. 1). The results demonstrate that there is almost no significant change in the activity of the catalyst, so, it could be used for at least five times successfully leading to high turn-over numbers (TONs).

3. Conclusions

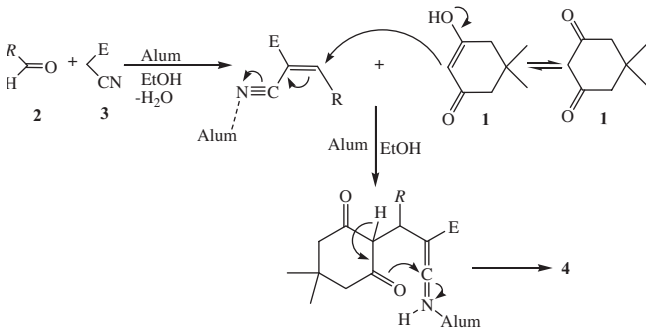
We described a successful strategy including, an efficient and convenient green synthesis, for the preparation of tetrahydrobenzo[b]pyran derivatives via a three-component reaction between dimedone, aldehydes, and active methylene compounds using $NH_4Al(SO_4)_2{\cdot}12H_2O$ (Alum) as catalyst at 80 °C. The method offers several advantages including high yield of products, using the inexpensive, reusable, nontoxic, and easily available $NH_4Al(SO_4)_2{\cdot}12H_2O$ catalyst, and an easy experimental workup procedure that makes it a useful process for the synthesis of tetrahydrobenzo[b]pyrans.

4. Experimental

Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-470 Spectrophotometer. ^1H NMR and ^{13}C NMR spectra were determined on Bruker 300 DRX Avance instrument at 300 and 75 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN–O-Rapid analyzer.



Scheme 1 Synthesis of tetrahydrobenzo[b]pyrans **4a-t**.



Scheme 2 Proposed mechanism for the formation of products **4a-t**.

4.1. General procedure

A mixture of dimedone (1 mmol), aldehyde (1 mmol), active methylene compounds (1 mmol) (malononitrile, ethyl and methyl cyanoacetate), 5 mL ethanol 96% and 0.2 g $NH_4Al(SO_4)_2{\cdot}12H_2O$ was heated with stirring at 80 °C for appropriate periods as indicated in Table 1. After completion of the reaction (TLC, ethyl acetate/*n*-hexane, 1/1), the crude product was recrystallized from ethanol.

4.1.1. Methyl 4-(2-amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromen-4-yl)benzoate (4k)

White powder; Mp 257–9 °C; IR (KBr) (υ_{max}, cm^{-1}): 3428, 2960, 2225, 1718, 1663; ^1H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 0.98 (3 H, s, Me), 1.11 (3 H, s, Me), 2.12 (1 H, d, J = 15.3 Hz, 8-HB), 2.22(1 H, d, J = 15.3 Hz, 8-HA), 2.48 (2 H, s, H-6), 3.87 (3 H, s, OCH_3), 4.80 (1 H, s, H-4), 7.37 (2 H, d, J = 7.5 Hz, arom), 7.92 (2 H, d, J = 7.5 Hz, arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 27.17, 29.28, 32.11, 32.19, 40.81, 50.53, 51.87, 115.01, 115.04, 128.21, 128.49, 129.50, 129.53, 149.30, 162.61, 167.05, and 196.39; MS (70 eV) m/z (%): 352 (M^+, 20), 273 (100), 217 (45), 161 (50), 152 (25), 133 (25), 115 (25), 83 (30), 77 (30), 59 (25), 41 (45); Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.03; H, 5.61; N, 7.83.

4.1.2. Ethyl 4-(4-(methoxycarbonyl)phenyl)-2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3- carboxylate (4l)

White powder; Mp 228–30 °C; IR (KBr) (υ_{max}, cm^{-1}): 3421, 2962, 1715, 1662; ^1H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 0.98 (3 H, s, Me), 1.13 (3 H, s, Me), 1.42 (3 H, t, J = 7.2 Hz, CH_3), 2.12 (1 H, d, J = 15.2 Hz, 8-HB), 2.22 (1 H, d, J = 15.2 Hz, 8-HA), 2.49 (2H, s, H-6), 3.98 (3 H, s, OCH_3), 4.41 (2 H, q, J = 7.2 Hz, OCH_2), 4.80 (1 H, s, H-4), 7.36 (2 H, d, J = 7.6 Hz, arom), 7.85 (2 H, d, J = 7.7 Hz, arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 15.47, 27.24, 29.29, 32.12, 32.21, 40.79, 50.52, 51.80, 52.56, 116.02, 128.25, 128.44, 129.53, 149.26, 153.48, 163.23, 166.11, 167.86, and

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Table 1 Synthesis of tetrahydrobenzo[b]pyrans **4** using $NH_4Al(SO_4)_2$ $12H_2O$ (Alum) as catalyst.

Products	R	E	Time (min)	Yield (%)[a]	Mp (°C)	Lit.mp (°C)
4a	Ph	CN	120	92	231–3	233–4 Sharanina and Shklover (1986)
4b	Ph	CO_2Et	120	83	192–4	190–2 Devi and Bhuyan (2004)
4c	4-$NO_2C_6H_4$	CN	130	93	177–9	177–8 Kaupp et al. (2003)
4d	3-$NO_2C_6H_4$	CN	130	90	212–13	210–12 Zhou et al. (2001)
4e	4-HOC_6H_4	CN	120	85	207–9	208–10 Tu et al. (2003)
4f	4-BrC_6H_4	CN	130	91	200–2	201–3 Wang et al. (2006)
4g	4-$MeOC_6H_4$	CN	130	90	190–2	192–4 Zhao et al. (2010)
4h	4-$(CH_3)_2NC_6H_4$	CN	130	91	207–9	208–10 Tu et al. (2003)
4i	4-ClC_6H_4	CN	120	94	217–9	218 Singh et al. (1996)
4j	4-ClC_6H_4	CO_2Et	120	93	258–9	256–9 Devi and Bhuyan (2004)
4k	4-Me $O_2CC_6H_4$	CN	130	95	257–9	–
4l	4-Me $O_2CC_6H_4$	CO_2Et	130	94	228–30	–
4m	4-Me $O_2CC_6H_4$	CO_2Me	130	93	240–2	–
4n	2-naphthyl	CN	130	85	253–5	–
4o	4-ClC_6H_4	CO_2Me	140	93	166–8	167–8 Zhao et al. (2010)
4p	4-MeC_6H_4	CN	130	90	221–3	223–5 Jin et al. (2004)
4q	4-$NO_2C_6H_4$	CO_2Et	140	85	182–4	181–3 Li et al. (2004)
4r	3-$NO_2C_6H_4$	CO_2Et	130	90	183–5	182–4 Li et al. (2004)
4s	4-$CF_3C_6H_4$	CN	130	95	220–2	219–21 Balalaie et al. (2006)
4t	3-$NO_2C_6H_4$	CO_2Me	130	90	190–2	190–2 Li et al. (2004)

[a] Isolated yields.

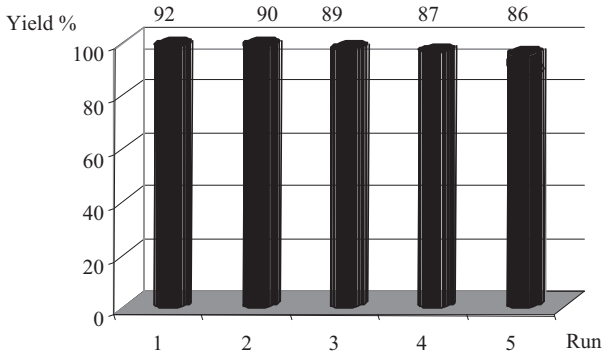

Figure 1 Five consecutive runs of the reaction of dimedone, benzaldehyde and malononitryl with Alum.

197.22; MS (70 eV) *m/z* (%): 399 (M^+, 50), 349 (50), 273 (100), 228 (25), 217 (35), 200 (25), 161 (30), 77 (30), 59 (30), 43 (30); Anal. Calcd. for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.04; H, 6.22; N, 3.40.

4.1.3. Methyl 4-(4-(methoxycarbonyl)phenyl)-2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carboxylate (4m)

White powder; Mp 240–2 °C; IR (KBr) (υ_{max}, cm^{-1}): 3428, 2961, 1718, 1658, 1618; ^1H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 0.98 (3 H, s, Me), 1.11 (3 H, s, Me), 2.15 (1 H, d, J = 15.3 Hz, 8-HB), 2.37 (1 H, d, J = 15.3 Hz, 8-HA), 2.47 (2 H, s, H-6), 3.88 (3 H, s, OCH_3), 3.97 (3 H, s, OCH_3), 4.80, (1 H, s, H-4), 7.38 (2 H, d, J = 7.6 Hz, arom), 7.90 (2 H, d, J = 7.5 Hz, arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 27.20, 29.32, 32.22, 32.30, 40.89, 50.88, 52.04, 52.60, 115.11, 128.23, 128.50, 129.60, 149.29, 153.88, 162.72, 166.06, 167.10, and 196.30; MS (70 eV) *m/z* (%): 385 (M^+, 35), 349 (60), 273 (100), 217 (35), 161 (30), 152 (30), 83 (35), 77 (20), 59 (35), 41 (40); Anal. Calcd. for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.32; H, 5.01; N, 3.51.

4.1.4. 2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(naphthalen-2-yl)-5-oxo-4H-chromene-3-carbonitrile (4n)

Cream powder; Mp 253–5 °C; IR (KBr) (υ_{max}, cm^{-1}): 3359, 3182, 2963, 2187, 1684, 1652; ^1H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 0.99 (3 H, s, Me), 1.12 (3 H, s, Me), 2.13 (1 H, d, J = 16.2 Hz, 8-HB), 2.23(1 H, d, J = 16.3 Hz, 8-HA), 2.49 (1 H, s, H-6), 3.54 (1 H, s, H-6), 4.46 (1 H, s, H-4), 7.37 (1 H, d, J = 7.5 Hz, arom), 7.49 (2 H, m, arom), 7.66 (1 H, s, arom), 7.80–7.90 (3 H, m, arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 27.22, 28.95, 32.27, 36.35, 50.45, 58.57, 112.90, 120.23, 125.97, 126.09, 126.65, 127.89, 128.12, 128.60, 132.51, 133.28, 143.01, 159.10, 163.04, and 195.99; MS (70 eV) *m/z* (%): 344 (M^+, 60), 327 (50), 291 (25), 277 (55), 217 (100), 165 (35), 152 (65), 127 (35), 83 (30), 66 (25), 41 (45); Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.63; H, 5.72; N, 8.02.

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References

Armetso, D., Horspool, W.M., Martin, N., Ramos, A., Seaone, C., 1989. J. Org. Chem. 54, 3069.

Azizian, J., Mohammadi, A.A., Karimi, A.R., 2003a. Synth. Commun. 33, 415.

Azizian, J., Karimi, A.R., Mohammadi, A.A., 2003b. Synth. Commun. 33, 387.

Azizian, J., Karimi, A.R., Arefrad, H., Mohammadi, A.A., Mohammadizadeh, M.R., 2003c. Mol. Diversity 6, 223.
Azizian, J., Mohammadi, A.A., Karimi, A.R., Mohammadizadeh, M.R., 2005. J. Org. Chem. 70, 350.
Balalaie, S., Bararjanian, M., Amani, A.M., Movassagh, B., 2006. Synlett 263, 2006.
Devi, I., Bhuyan, P.J., 2004. Tetrahedron Lett. 45, 8525.
Domling, A., Ugi, I., 2000. Angew. Chem., Int. Ed. Engl. 39, 3321.
Green, G.R., Evans, J.M., Vong, A.K., 1995. In: Katrizky, A.R., Rees, C.W., Scriven, E.F.V. (Eds.), . In: Comprehensive Heterocyclic Chemistry II, vol. 5. Pergamon Press, Oxford, p. 469.
Jin, T.S., Wang, A.Q., Zhang, J.S., Zhang, F.S., Li, T.S., 2004. Chin. J. Org. Chem. 2004, 1598.
Jin, T.S., Wang, A.Q., Wang, X., Zhang, J.S., Li, T.S., 2004. Synlett 871.
Kamaljit, S., Jasbir, S., Harjit, S., 1996. Tetrahedron 52, 14273.
Kaupp, G., Naimi-Zamal, M.R., Schmeyers, J., 2003. Tetrahedron 59, 3753.
Konkoy, C.S., Fick, D.B., Cai, S.X., Lan, N.C., Keana, J.F.W., 2001. PCT Int. Appl. Wo 0075123, 2000, Chem Abestr. 134, 29313a.
Li, J.T., Xu, W.Z., Yang, L.C., Li, T.S., 2004. Synth. Commun. 34, 4565.
Mohammadi, A.A., Azizian, J., Hadadzahmatkesh, A., Asgharigan-jeh, M.R., 2008. Heterocycles 75, 947.
Rathod, S., Arbad, B., Lande, M., 2010. Chin. J. Catal. 31, 631.
Sharanina, L.G., Shklover, V.E., 1986. J. Org. Chem. 22, 1185.
Shi, D.Q., Zhang, S., Zhuang, Q.Y., Tu, S.J., Hu, H.W., 2003. Chin. J. Org. Chem. 23, 877.
Singh, K., Singh, J., Singh, H., 1996. Tetrahedron 52, 14273.
Sun, H.B., Hua, W.Y., Chen, L., Peng, S.X., Wang, T., Liu, G.Q., 1997. Chem. J. Chin. Univ. 18, 730.
Tu, S.J., Jiang, H., Zhuang, Q.Y., Miu, C.B., Shi, D.Q., Wang, X.S., Gao, Y., 2003. Chin. J. Org. Chem. 23, 488.
Wang, L.M., Shao, J.H., Tian, H., Wang, Y.H., Liu, B., 2006. J. Fluo. Chem. 127, 97.
Weber, L., Illegen, K., Almstetter, M., 1999. Synlett 366, 1999.
Zhao, L.Q., Li, Y.Q., Chen, L., Zhou, B., 2010. Chin. J. Org. Chem. 30, 124.
Zhou, J.F., Tu, S.J., Gao, Y., Ji, M., 2001. Chin. J. Org. Chem. 21, 742.

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